REMARKS

The Applicants acknowledge receipt of the October 21, 2004 Office Action, and have the following comments.

35 USC §112(1) Enablement Rejection

Claims 11-16 have again been rejected as allegedly lacking enablement. Applicants note and acknowledge that the Examiner has not applied this rejection against claim 17.

The Applicants hereby incorporate by reference the traversal of this rejection made in the last Reply.

The stated rationale for this rejection is that the person of ordinary skill in the art would not know how to "make and use the alpha subunits recited in the instant claims" because there is allegedly insufficient guidance to direct a person of skill in the art to select an alpha subunit as "essential" for inhibiting VEGF-dependent angiogenesis. See August 25, 2004 Office Action, page 3. Applicants respectfully traverse this rejection.

The Examiner has responded that "Applicant appears to mischaracterize the rejection of record", when arguing that none of the pending claims are so limited, because "the Examiner never points to the claims when discussing the 'VEGF-dependent angiogenesis'" Office Action at page 2.

Applicants are not quite sure how to respond to this statement. On page 3 of the prior Office Action the Examiner states that "[t]here is insufficient guidance to direct a person of skill in the art to select [a] particular alpha integrin subunit as essential for inhibiting angiogenesis dependent VEGF [sic]". Based on this statement Applicants believe they are justified in believing that the Examiner bases part of the rationale for the rejection on his belief that VEGF-dependent angiogenesis is somehow an essential feature of the claims.

Moreover, although the Examiner says that the Applicants have mischaracterized the rejection, the Examiner continues "further . . . it is clear that the specification indeed refers to "VEGF driven agoniogenic response". Applicants do not, of course, dispute this - however, Applicants claims the subject matter of the pending claims rather than a particular embodiment taken from the specification.

In making the current enablement rejection the Examiner continues to argue the relevance of a number of references published after the priority date of this application, among them Bergreson et al., *Biochem. J.* 2003, Ratnikov et al., *J. Biol. Chem.* 277:7377-7385 (2002); and Zhang et al., *Invest. Ophthal. Vis. Sci.* 43:955-962 (2002). As this rejection is not a prior art rejection, the function of these citations in the context of an enablement rejection is not thought to be germane to the question of enablement.

Enablement requires that the specification be sufficient to permit a person of ordinary skill in the art to make and use the claimed invention without undue experimentation. The present specification sets forth various methodologies for the correlation of angiogenesis (in this case, corneal neovascularization) with MT-MMP1 activation of specific alpha subunits. Among these methods are anti-alpha subunit-specific antibody staining of developing vasculature (see, e.g., pages 12, 13, 28 and 29) and gelatin zymography, (pages 14 and 15). Antibodies to the known alpha subunits are commercially available, so the "making" of such antibodies or, by definition, identification of their specific antigens is a matter of routine. All that remains to be done is to incubate the cells, tissue, subunits or animal with the agent to be tested.

The Office Action appears to argue, because a single model system of angiogenesis was studied in the experiments disclosed in this specification (corneal angiogenesis, a VEGF-mediated angiogenic pathway which implicates α_VB5 and other integrin subunits), that Applicants disclosure is somehow inconsistent with the literature concerning other pathways, such as the bFGF-mediated angiogenesis pathway (which implicates α_VB3, among other integrin subunits). This not the case – Applicants have claimed a generally useful method for the detection of angiogenesis associated with MT-MMP1 activation of alpha integrin subunits.

Moreover, it is well established that a patent need not teach, and preferably omits, what is well known in the art. *In re Wright*, 27 USPQ2d 1510 (Fed. Cir. 1993). Having disclosed facile methods for testing which alpha subunits capable of MT1-MMP activation are involved in angiogenesis, the person of ordinary skill can perform these tests easily and without undue experimentation.

For the reasons stated above, Applicants believe the claims are free of this rejection, and therefore respectfully ask the Examiner to reconsider and withdraw this rejection.

35 USC §112(1) Written Description Rejection

Claims 11-16 again stand rejected over 35 USC 112(1) as allegedly lacking sufficient written description in the specification as filed. Applicants note that claim 17 is no longer so rejected. Applicants respectfully traverse the rejection of claims 11-16.

Applicants incorporate by reference their traversal of this rejection in the last Reply.

The Examiner summarily concludes, with no rationale or evidence for his findings, that "Applicant is not in possession of a method for screening an agent which inhibits n angiogenic response . . ." and "Applicant is not in possession for determining whether an agent will inhibit an angiogenic response."

Section 112 of Title 35 of the US Code requires that the specification contain a written description of the invention. The Court of Appeals for the Federal Circuit has recently rearticulated the basic rule that

> [t]he purpose of the written description requirement is to prevent an applicant from later asserting that he invented that which he did not; the applicant for a patent is therefore required to "recount his invention in such detail that his future claims can be determined to be encompassed within his original creation." . . . [*Vas-Cath, Inc. v. Mahurkar*, 19 USPQ2d 1111, 1115 (Fed. Cir. 1991)]. Satisfaction of this requirement is measured by the understanding of the ordinarily skilled artisan. *Lockwood v. Am. Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997) . . . .

Amgen, Inc. v. Hoescht Marion Roussel, Inc., 65 USPQ2d 1385, 1397 (Fed. Cir. 2003).

The Office Action also cited the *PTO Final Guidelines on Written Description Requirement* (66 Fed. Reg. 1099 (Friday, January 5, 2001)) (the "Guidelines") in support of the rejection of these claims. In particular, the Office Action notes the Guidelines at 1106, third column. However, a review of this citation reveals that the indicated passage concerns claims drawn to claims to a genus of different species. Applicants do not claim a genus of different species, they claim a single general method; thus the cited passage is not applicant to the present invention.

The Examiner replies, with no citation to supporting case law or evidence, that "the instant methods require the use of products, and if the products do not meet the

written description requirements [sic], then it follows that the instant method does not meet the written description requirement". Office Action at page 5, not only do Applicants strongly disagree that such a conclusion necessarily follows, but maintain that such a conclusion is simply wrong.

As an example, the polymerase chain reaction (PCR) is a method of replicating specific regions of a given DNA by using upstream and down stream oligonucleotide primers with the enzyme DNA polymerase in a series of annealing and melting steps.

It is now established that a written description of a nucleic acid requires a description of the structure of the nucleic acid" that is, its nucleotide sequence. See e.g., *Regents of the University of California v. Eli Lily & Co.*, 43 USPQ2d 1398 (Fed. Cir. 1997). If the Examiner's assertion above were correct, and methods could only be adequately described if the elements of the method "passed" the written description test, the general PCR method would be unpatentable because one cannot practically provide the nucleotide sequence of each and every possible primer or template DNA for which the PCR method is applicable.

Of course, the rule articulated above is not the law, and the general PCR method has been the subject of numerous patents. If the Examiner proposes to repeat this ground of rejection, Applicants respectfully request that case law or evidence supporting the Examiner's position regarding the applicability of this rule be provided.

The Examiners' conclusion that Applicants were not is "possession" of the claimed method appears to be based on a misinterpretation of the term "possession" in this context. Although word "possession" can be interpreted to mean "actually reduced to practice", in written description jurisprudence "possession" is similar to 'conception".

For example, the Guidelines indicate that in most cases "the statement that 'an originally filed claim i[such as this one] is its own written description' is borne out because the claim language conveys to others of skill in the art that the applicant was "in possession' of what is claimed." (Guidelines, answer to comment 3, at 1100 (emphasis added)), and in all cases a strong presumption exists that an adequate written description of the invention originally claimed exists when the application is filed. *Id.* at 1105. This means that the Examiner must establish a prima facie case supporting a written description rejection by clear and convincing evidence; this the Examiner has not done.

For the above-referenced reasons the Applicants respectfully request reconsideration and withdrawal of the rejection.

Rejection Pursuant to 35 USC §102(b)

Claims 11 and 14-17 were again rejected as allegedly anticipated over Klotz et al., GRAEFES ARCH. CLIN. EXP. OPHTHALMOL. 238:88-93 (January 2000) "as evidenced by" Zhang et al., *supra*. Applicants traverse this rejection for the following reasons:

In order to anticipate, a single reference must disclose within its four corners each and every limitation of the challenged claim. See e.g., *Scripps Clinical & Research Foundation v. Genentech*, Inc. 18 USPQ2d 1001 (Fed. Cir. 1991). Moreover, an anticipatory reference must enable the claimed invention. *Id.*

The Examiner has stated that Zhang (which is not prior art to the present application) is used to show that an undisclosed characteristic is present in Klotz.

Even assuming for the same of argument that MT1-MMP is inherently present in the corneal tissue of Klotz (which Applicants do not admit), Applicants submit that Klotz does not disclose correlating inhibition of said increase in integrin α subunit activation with the ability of the agent to inhibit angiogenesis. Instead, Klotz directly measures the angiogenic response of corneal tissue to a test agent, and does not acknowledge the existence of MT1-MMP-cleaved species of the integrin alpha subunits at all.

By contrast, what is presently claimed is a screening method that can be used in the absence of, or in tandem with, a direct measurement of the angiogenic response. The focus of the claimed method is the activation or lack thereof of an integrin alpha subunit. As indicated in the specification, an inhibition of activation can be assayed by methods including detection of the appearance of a lower molecular weight integrin species due to MT1-MMP cleavage thereof, or of the reduction of the higher molecular weight non-activated alpha subunit.

The Examiner argues the direct measurement of angiogenesis is the "correlating step" claimed in the present claims, stating that such would be "immediately apparent to one of skill in the art" However, how could such a person "immediately" know this without prior knowledge of the observation of the "increase in integrin α subunit activation" in such correlating step?

Moreover, Klotz does not disclose observing the extent of integrin α subunit activation, an element of the present claims.

Rejection pursuant to 35 USC §103(a)

Claims 11-13 were rejected as allegedly anticipated by Klotz et al., supra and Deryugina et al., cited as reference AB in the IDS filed in the present case. Again, the PTO cites a post-filing reference, Zhang et al, apparently as alleged evidence of inherency of the missing MT1-MMP element in Klotz, although this is not entirely clear in the Office Action.

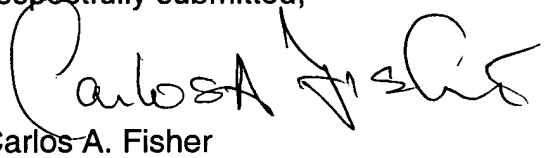
None of the references, either alone or in combination, acknowledge or suggest the existence of MT1-MMP-cleaved species of the integrin alpha subunits, much less observing changes in the activation of such species activation as is claimed.

Since the present claim as a whole is not even suggested in the two references or their combination, Applicants respectfully request that the Examiner reconsider and withdrawn the present rejection.

CONCLUSION

The Commissioner is hereby authorized to use Deposit Account 01-0885 for the extenaion of time payment and any fee properly due.

Respectfully submitted,



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